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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,095	06/06/2002	Derek L Stemple	18921-001	9297

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,095	STEMPLE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☒ Claim(s) *1, 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-13) in the reply filed on July 28, 2004 is acknowledged. The traversal is on the ground(s) that Groups I and II are related as product and process of use and would not be an undue burden to examine both sets of claims. This is not found persuasive because searching for the product used in a method does require a different search. For example, in an instant case, the immobilized polymerase system can be used in other methods, and, conversely, it is not required for the method of Group I. Therefore, searching for prior art anticipating or suggesting method claims 1-13 may not uncover art anticipating or suggesting product claims 14-23.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 14-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 28, 2004.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In the Declaration Applicants claim priority to the co-pending application No. 09/266,187, filed March 10, 1999, without providing the relationship between the two applications and without providing a reference to the 09/266,187 application in the first sentence of the specification.

Claim Objections

5. Claim 1 is objected to because of the following informalities: there is a period in the middle of step c), after "group". Appropriate correction is required.

6. Claim 2 is objected to because of the following informalities: there is a period after "claim 1" in line 1. Appropriate correction is required.

Claim Interpretation

7. The term "immobilizing a polymerase on a solid support" is interpreted as binding the polymerase to a solid support either directly, for example, covalently, or indirectly, via binding of the polymerase to a nucleic acid attached to a solid support, for example. Applicants did not provide a definition of "immobilized polymerase", and only the following description (specification, page 3, first two lines of the fourth paragraph): "... a plurality of polymerase molecules is immobilized on a solid support through a covalent or non-covalent interaction".

8. The order of steps in the method of claim 1 is given weight because of the phrase in the preamble "comprising the sequential steps of". For that reason there was no rejection made under

35 U.S.C. 102(b) over Ross et al., who do not teach immobilization of the polymerase prior to contacting the polymerase with a nucleic acid sample and primers.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ross et al. (WO 91/06678) and Williams (U.S. Patent No. 6,255,083 B1).

A) Regarding claim 1, Ross et al. teach a method of nucleic acid sequencing, the method comprising:

(b) providing a nucleic acid sample and a plurality of different oligonucleotide primers, wherein the nucleic acid sample hybridizes to an oligonucleotide primer (Ross et al. teach providing a nucleic acid template and primers, where the nucleic acid hybridizes to an oligonucleotide primer (Fig. 1A and 1B; page 10, lines 32-35; page 11, lines 1-20).);

(a) immobilizing a polymerase on a solid support (Ross et al. teach that either the primer or the template are immobilized on solid support (Fig. 1A and 1B; page 10, lines 32-35; page 11, lines 1-20; page 32, lines 10-35; page 33, 34). Ross et al. teach addition of a polymerase to the immobilized template-primer complex, therefore they teach immobilizing the polymerase indirectly on a solid support (Fig. 1A and 1B; Fig. 2; page 12, lines 11-14 and 21-27).);

(c) providing four different nucleotides, each nucleotide being differentially-labeled with a detachable labeling group and blocked at the 3' portion with a detachable blocking group, wherein the polymerase extends the primer hybridized to the nucleic acid sample with the differentially-

labeled nucleotide that is complementary to the sample nucleic acid (Ross et al. teach providing four differently labeled and blocked dNTPs to the reaction zone with the templete, primer and polymerase (page 12, lines 15-18 and 29). Ross et al. teach a detachable 3'-blocking group (page 20, lines 25-34; page 21, 22; page 23, lines 1-25) and a detachable labeling group which is bound to the blocking group (page 14, lines 19-26; page 21, lines 4-8 and 28-31), or to the base of the nucleotide (page 27, lines 33-36; page 28, 29). The polymerase extends the primer with a labeled nucleotide complementary to the sample nucleic acid (page 12, lines 22-27).);

(d) removing nucleotides that have not been incorporated in the primer (Ross et al. teach removal of unreacted (= not incorporated) nucleotides (page 12, lines 29-34).);

(e) detecting the labeled nucleotide incorporated into the elongating primer, thereby identifying the complement of the labeled 3'-blocked nucleotide (Ross et al. teach identifying the complement of the labeled 3'-blocked nucleotide by detecting the label attached to it (page 13, lines 1-13; page 26-28).);

(f) separating the 3' blocking group and the labeling group from the incorporated nucleotide (Ross et al. teach separating the blocking group and the labeling group from the incorporated nucleotide (page 13, lines 14-22; page 23, lines 28-35; page 24, 25; page 27, lines 33-36; page 28).);

(g) removing the separated 3' blocking group and the separated labeling group of step (f) (Ross et al. teach removing the separated 3' blocking group and the labeling group (page 13, lines 22-24).);

(h) confirming separation and removal of the 3' blocking group from the nucleotide incorporated in the primer (Ross et al. teach identifying the complement of the labeled 3'-blocked nucleotide by detecting the label attached to it (page 13, lines 1-13; page 14, lines 30-34; page 26-28), therefore, since it is the labeled group attached to the blocking group that is detected and it is

removed before detection, Ross et al. inherently teach confirming separation and removal of the blocking group from the nucleotide incorporated into the primer.); and

(i) repeating steps (c) through (g) until either no new nucleotides are incorporated in step (c) or the 3' blocking group persists in not being separated and removed in steps (f) and (g), whereby the order in which the labeled nucleotide in step (d) are detected corresponds to the complement of the sequence of at least a portion of the nucleic acid sample (Ross et al. teach repeating the steps until the complementary chain has been completed, thereby providing the sequence of the nucleic acid sample (page 13, lines 30-35).).

Regarding claim 2, Ross et al. teach separation of the blocking group and the labeling group by photochemical activation (page 25, lines 4-12).

Regarding claim 3, Ross et al. teach separation of the blocking group and the labeling group by chemical reaction (page 24; page 25, lines 1-3; page 28, lines 19-35; page 38, lines 30-36; page 39, lines 1-9) or enzymatically (page 25, lines 14-25; page 39, lines 12-22).

Regarding claim 4, Ross et al. teach fluorescent labels (page 13, lines 4-8; page 21, lines 29-31; page 26, lines 17-26).

Regarding claim 5, Ross et al. teach attachment of the labeling group to the blocking group (page 14, lines 19-26; page 21, lines 4-8 and 28-31).

Regarding claims 6 and 8, Ross et al. teach a 2-nitrobenzyl group (page 21, line 26).

Regarding claim 7, Ross et al. teach attachment of the labeling group to the base of the nucleotide with a detachable linker (page 27, lines 33-36; page 28, lines 1-4 and 19-35).

Regarding claims 9 and 10, Ross et al. teach DNA polymerases, Taq (=DNA polymerase from Thermus acquaticus) and Klenow fragment of DNA polymerase I (page 19, lines 17, 18).

Regarding claims 9 and 12, Ross et al. teach an AMV reverse transcriptase (page 19, lines 1, 18).

B) Ross et al. do not teach a polymerase immobilized directly on a solid support, an RNA polymerase or detection of labeled nucleotides by total internal reflection fluorescence microscopy (TIFR), photon confocal microscopy, surface plasmon resonance and fluorescence resonance energy transfer (FRET).

B) Regarding claim 1, Williams teaches a method of nucleic acid sequencing, the method comprising:

(a) immobilizing a polymerase on solid support (Williams teaches immobilizing a nucleic acid polymerase onto a solid support (col. 2, lines 16-19).)

(b) providing a nucleic acid sample and a plurality of different oligonucleotide primers, wherein the nucleic acid sample hybridizes to an oligonucleotide primer (Williams teaches providing a nucleic acid template and primers, where the nucleic acid hybridizes to an oligonucleotide primer (col. 2, lines 21-26).);

(c) providing four different nucleotides, each nucleotide being differentially-labeled with a detachable labeling group, wherein the polymerase extends the primer hybridized to the nucleic acid sample with the differentially-labeled nucleotide that is complementary to the sample nucleic acid (Williams teaches providing four differently labeled dNTPs and the polymerase extending the primer to create complement of the target nucleic acid (col. 2, lines 26-32).);

(e) detecting the labeled nucleotide incorporated into the elongating primer, thereby identifying the complement of the labeled 3'-blocked nucleotide (Williams teaches identifying the complement of the labeled nucleotide by detecting the label attached to it (col. 2, lines 32-35; col. 4, lines 4-22).).

Regarding claims 9 and 11, Williams teaches T7 RNA polymerase and E. coli RNA polymerase (col. 10, lines 65, 66).

Regarding claim 13, Williams teaches detection of fluorescently labeled pyrophosphates using TIFR (col. 12, lines 23-39 and 59-67).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the RNA polymerase of Williams in the method of Ross et al. The motivation to do so, provided by Williams, would have been that the T7 RNA polymerase and RNA polymerase from E. coli had a fidelity of at least 99% and a processivity of at least 20 nucleotides (col. 10, lines 59-62).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the TIFR detection method of Williams in the sequencing method of Ross et al. The motivation to do so, provided by Williams, would have been that TIFR detected single molecules with a signal-to-noise ratio of 12:1 at visible wavelengths (col. 12, lines 64-67).

It would have been *prima facie* obvious to have used an immobilized polymerase of Williams in the method of Ross et al. The motivation to do, provided by Williams, would have been that immobilization of polymerases allowed for analysis of single nucleic acid molecules which were obtained directly from an organism without the need for cloning or amplification and multiple nucleic acids were sequenced simultaneously (col. 1, lines 54-63), and, as stated by Williams (col. 13, lines 63-67): "Tethering of the polymerase, rather than the target nucleic acid (template) is convenient because it provides for a continuous sequencing process where one immobilized enzyme sequences many different DNA molecules.".

11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 25, 2004

Teresa Strzelecka
Teresa Strzelecka
Patent Examiner